In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 14-952V

Filed: April 12, 2021

ELIZABETH NICOLE ROBINSON, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	TO BE PUBLISHED Special Master Katherine E. Oler Ruling; Multiple Sclerosis; Flu Vaccine

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Darryl Wishard, U.S. Department of Justice, Washington, DC, for Respondent

ENTITLEMENT RULING[1]

On October 6, 2014, Elizbeth Nicole Robinson ("Ms. Robinson" or "Petitioner") filed a petition pursuant to the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10.[2] ("Vaccine Act" or "the Program") alleging that the influenza vaccination she received on October 18, 2011 caused her to develop relapsing-remitting multiple sclerosis ("MS"), neurogenic bladder, and paresthesias. Pet. at 1, ECF No. 1.

Upon review of the evidence submitted in this case, I find that Petitioner has met her burden in showing that the flu vaccination she received on October 18, 2011 caused her to develop MS. She is therefore entitled to compensation under the Vaccine Act.

[1] This Ruling will be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the Ruling will be available to anyone with access to the internet**. As provided in 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the Ruling's inclusion of certain kinds of confidential information. To do so, each party may, within 14 days, request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, this Ruling will be available to the public in its present form. *Id.*

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (1986). Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

I. Procedural History

Petitioner filed a petition on October 6, 2014 in which she alleged the influenza vaccination she received on October 18, 2011 caused her to develop vaccine-induced relapsing-remitting multiple sclerosis, neurogenic bladder, and paresthesias. Pet. at 1, ECF No. 1. On December 29, 2014, Petitioner filed a Statement of Completion. ECF No. 13. On October 15, 2015, Petitioner filed an expert report from Dr. Lawrence Steinman. Ex. 13, ECF No. 25. On April 6, 2016, Respondent filed a Rule 4(c) Report and an expert report from Dr. Timothy Vartanian. Resp't's Rep.; Ex. A.

On May 19, 2016, Petitioner filed a status report indicating that he was "uncertain how to provide adequate information to move this case forward without guidance from a life care planner." Pet'r's Status Rep. on 5/19/2016, ECF No. 39. On May 24, 2016, Special Master Hastings issued an order authorizing Petitioner's counsel to hire a life care planner for settlement purposes. ECF No. 40. Petitioner filed multiple status reports providing updates on the hiring on a life care planner and the preparation of a settlement offer. See Pet'r's Status Reps. on 11/15/2016; 1/30/2017; 3/2/2017; 5/2/2017; 7/3/2017; 8/28/2017. On December 7, 2017, Respondent filed a status report stating he was not interested in settlement discussions and requested that an entitlement hearing be scheduled. Resp't's Status Rep. on 12/7/2017, ECF No. 59. An entitlement hearing was set for May 21 and 22, 2019. *See* non-PDF Scheduling Order on 3/28/2018.

On January 20, 2019, this case was referred to Special Master Sanders for ADR. ECF No. 60. The case was removed from ADR on March 26, 2019. ECF No. 63.

I held an entitlement hearing on May 21 and 22, 2019 in Washington, DC. On July 8, 2019, Respondent filed a supplemental expert report by Dr. Vartanian. Ex. W, ECF No. 78. Petitioner filed employment records regarding vaccination on July 22, 2019. Ex. 41, ECF No. 83. Petitioner filed additional medical records on July 22, 2019; September 6, 2019; September 17, 2019. *See* Exs. 40, 42, 48-51. Petitioner also filed supplemental expert reports from Dr. Steinman on September 6, 2019. Exs. 43, 47. The parties filed post-hearing briefs on May 1, 2020. (ECF Nos. 99, 100) and a joint status report stating the record was complete on May 27, 2020. ECF No. 101. This case is now ripe for adjudication.

II. Medical Records

A. Petitioner's Health Prior to the Allegedly Causal Vaccination

Petitioner was in good health prior to the allegedly causal vaccination. Petitioner suffered from asthma and seasonal allergies and began sublingual immunotherapy ("SLIT")[3] in August

[3] SLIT stands for sublingual immunotherapy. Sublingual is "beneath the tongue; called also hypoglossal and subglossal." *Sublingual*¸ DORLAND'S MEDICAL DICTIONARY ONLINE (hereinafter "DORLAND'S"), https://www.dorlandsonline.com/dorland/definition?id=47717 (last visited on March 19, 2021). Immunnotherapy is "a general term encompassing active and passive immunization, treatment with immunopotentiators and immunosuppressants, hyposensitization for allergic disorders, stem cell

2011. *See* Ex. 3 at 58-61. Petitioner received the influenza vaccination on October 18, 2011. Ex. 2 at 1.

B. Petitioner's Health after the Allegedly Causal Vaccination

Petitioner began to experience left hand numbness on October 31, 2011. Ex. 3 at 72; Ex. 12 at 2. On November 14, 2011, Petitioner was seen by Dr. Kevin Suttmoeller of the University of Missouri Health System for numbness in three of her fingers. *Id.* Dr. Suttmoeller's impression was that Petitioner had left carpal tunnel syndrome. *Id.* at 76.

On November 28, 2011, Petitioner underwent an EMG/NCV (electromyography and nerve conduction velocity) test that ruled out carpal tunnel syndrome. Ex. 3 at 44, 74, 76. The medical records note that Petitioner was positive for Tinel's sign[4], but otherwise tested normal. *Id.* at 44.

On February 1, 2012, Petitioner returned to Dr. Suttmoeller "for worsening numbness and tingling". Ex. 3 at 77. On February 21, 2012, Petitioner saw Dr. Miguel Arista, a neurologist, complaining of "numbness and tingling in different parts of the body and vertigo." *Id.* at 85. Dr. Arista ordered an EMG, nerve conduction study (NCS), a brain MRI with contrast, and a variety of labs. *Id.* at 88. The MRI, performed on March 21, 2012, revealed a "[s]ingle tiny nonenhancing focus of T2 hyperintense white matter signal." *Id.* at 47. The MRI also revealed "minimal thickening and enhancement of the proximal left optic nerve." *Id.* at 53.

On June 29, 2012, Petitioner had a follow up appointment for her SLIT treatment. Ex. 3 at 91. Petitioner stated she had no complaints but had to use some Benadryl on and off for two weeks in the beginning of summer but wanted to continue SLIT therapy. *Id.* Petitioner was diagnosed with allergic conjunctivitis and allergic rhinitis. *Id.* at 93.

On August 2, 2012, Petitioner visited the University of Missouri Eye Clinic as a walk-in patient complaining of "pain when [she] moves her OS [oculus sinister or left eye] in all ROM's started 2 wks ago also see's [sic] blue sports OU [oculus uterque or both eyes] off + on. (circles)". Ex. 10 at 1. It was the treating physician's impression that Petitioner may have optic neuritis. *Id.* at 2.

On August 2, 2012, Petitioner was admitted to the University of Missouri ER. Ex. 3 at 1-9. Petitioner had undergone an outpatient MRI earlier in the day and was called by an ophthalmologist telling her she had neuritis and that she should go to the ER for admission to the hospital. *Id.* at 1. An MRI revealed:

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transplantation, and thymus implantation." *Immunotherapy*, DORLAND'S, https://www.dorlandsonline.com/dorland/definition?id=24943 (last visited on March 19, 2021)

[4] Tinel's is "a tingling sensation in the distal end of a limb when percussion is made over the site of a divided nerve. It indicates a partial lesion or the beginning regeneration of the nerve." *Tinel sign*, DORLAND'S, https://www.dorlandsonline.com/ dorland/definition?id=106510 (last visited on December 14, 2020).

Impression:

1. Subtle tiny abnormal signal is noted in the deep white matter of the brain in the periventricular region. Possibility of multiple sclerosis cannot be excluded. Requires clinical correlation.
2. Minimal thickening and enhancement of the left optic nerve raises the possibility of left optic neuritis.
3. No evidence of acute infarction.

Id. at 6. Both lesions were notable for faint enhancement. *Id.* at 5. On August 3, 2012, Petitioner underwent a lumbar puncture. *Id.* at 18-19. Petitioner was discharged on August 5, 2012 in stable condition after being treated with IV Solu-Medrol for three days. *Id.* at 16-17.

On August 7, 2012, Petitioner was seen by Dr. Suttmoeller for a headache, nausea, and vomiting. Ex. 3 at 95. Petitioner had been "admitted over the weekend for optic neuritis" and had a lumbar puncture and MRI done. *Id.* Petitioner was treated with diazepam and was instructed to increase hydration and keep a light diet. *Id.* at 98.

On August 10, 2012, Petitioner underwent an MRI of the cervical spine, which revealed a "tiny T2 hyperintense focus noted in the spinal cord in the left side of the level of C4 may be artifactual. No definite enhancement of the cord noted after contrast." Ex. 3 at 25.

On August 24, 2012, Petitioner was seen by Dr. Robert Burger, a neurologist at University of Missouri Neurology Clinic. Ex. 3 at 30-33. A lumbar puncture was performed and revealed 12 oligoclonal bands in the cerebral spinal fluid (and not in the serum). *Id.* at 31. Dr. Burger indicated, "At this point, given that she has shown to have central nervous system lesions separated both in space and time along with a positive spinal fluid, I think she has clinically definite multiple sclerosis." *Id.* at 33.

On August 27, 2012, Petitioner was seen by Dr. Elizabeth Wilson at Women's Health Associates, with a complaint of "bladder urgency". Ex. 5 at 13-15. Dr. Wilson noted that Dr. Burger had given her medication for neurogenic bladder. *Id.* at 13.

On September 5, 2012, Petitioner returned to Dr. Suttmoeller for frequent urination. Ex. 3 at 35-38. Dr. Suttmoeller ordered a CT scan and prescribed pyridium and doxycycline. *Id.* at 38.

On October 24, 2012, Petitioner was exempted from the seasonal flu vaccine by Dr. Burger, citing "hand numbness/tingling 2 wks after flu vaccine improving 5-6 wks later. Subsequently diagnosed with MS. Notified per e-mail this is a permanent exemption." Ex. 2 at 1.

On November 13, 2012, Petitioner visited Dr. James Klaas, a neurologist at the Mayo Clinic. Ex. 4 at 24-28. Dr. Klaas reviewed approximately 100 pages of Petitioner's past medical records and summarized her symptoms. *Id.* at 24-27. Dr. Klaas' impression was that Petitioner had relapsing/remitting multiple sclerosis, left optic neuritis, a neurogenic bladder, constipation, insomnia, fatigue, and paresthesias. *Id.* at 27. Dr. Klaas recommended high-dose interferon therapy as treatment but Petitioner and her husband decided to discuss this before initiating treatment. *Id.*

Dr. Klaas also recommended that Petitioner stop taking magnesium citrate and chlorella supplements, end her gluten-free diet, and take a multivitamin and a vitamin D replacement. *Id.* at 28. It was unclear to Dr. Klaas if the insomnia and fatigue were related to Petitioner's MS but recommended lifestyle changes such as moderate exercise and good sleep hygiene. *Id.* Petitioner was seen by Dr. Orhun Kantarci as well, who confirmed Dr. Klaas' findings. *Id.* at 19-21. Dr. Kantarci ordered additional lab work for Petitioner to confirm MS. *Id.* at 19. Dr. Kantarci also recommended another MRI in three months to see if there was a continued increase in lesions. *Id.* at 20. Treatment would be more pressing if her disease progression was active. *See id.*

On the same day, Petitioner visited Michelle Bouquet, PA for a urology consult. Ex. 4 at 15. Petitioner stated she was suffering from dysuria and a cramping sensation, had seen improvement, but continues to suffer from frequent urination and urinary urgency. *Id.* In particular, Petitioner stated the hours between 11 a.m. and 7 p.m. are better but symptoms worsen at night. *Id.* PA Bouquet recommended that Petitioner keep a two-day voiding diary.

On January 18, 2013, Petitioner returned to Dr. Kantarci for a follow-up appointment. Ex. 4 at 5-6. Dr. Kantarci noted her bloodwork provided no explanation other than MS for her symptoms. *Id.* at 5. The records note that there were "a couple of new brain lesions that are T2 hyperintense," which combined with her August 2012 MRI, indicated her "disease is active." *Id.* Petitioner discussed reservations with injectable medication and decided to discuss these concerns with her local neurologist, Dr. Burger, before initiating treatment. *Id.*

On July 2, 2013, Petitioner had a yearly checkup with Dr. Suttmoeller. Ex. 3 at 39-42. Petitioner reported she had been to the Mayo Clinic for relapsing remitting multiple sclerosis and a continuation of her symptoms. *Id.* at 39.

On October 24, 2013, Petitioner was exempted from the flu vaccine once again. Ex. 2 at 1.

On February 6, 2014, Petitioner visited the Illinois Eye Center complaining of right eye pain that had lasted seven days. Ex. 7 at 7-8. Pain occurs during movement of the eyeball and Petitioner was seeing blue flashes. *Id.* at 8. Petitioner also complained that her vision "fluctuates". *Id.* Petitioner was instructed to stop prednisone. *Id.* at 7. On February 13, 2014, Petitioner returned to the Illinois Eye Center for eye pain and worsening vision. *Id.* at 3-4. Petitioner complained of five days of eye pain and decreased vision. *Id.* at 4. Petitioner was assessed with optic neuritis and MS. *Id.* at 3.

On February 28, 2014, Petitioner visited Dr. Dennis Garwacki, a neurologist at the Illinois Neurological Institute. Ex. 8 at 1-2. Dr. Garwacki noted that Petitioner had "Multiple sclerosis with two clinical attacks" and recommended treatment to prevent long-term disability. *Id.* at 2. Dr. Garwacki also recommended she increase her vitamin D intake for her low vitamin D levels. *See id.* Petitioner expressed hesitation to start medication to treat her MS but Dr. Garwacki felt like he had convinced her. *See id.*

On June 30, 2014, Petitioner returned to the Illinois Neurological Institute for a four-month follow-up. Ex. 8 at 3-4. Petitioner had not begun treatment for her MS and did not increase her vitamin D supplemental intake level per Dr. Gawacki's recommendation. *Id.* at 3.

No other medical records filed were pertinent to the issues to be addressed in this case.

III. Fact Testimony

A. Ms. Elizabeth Nicole Robinson, Petitioner

Petitioner testified that she lives with her husband and three children in Peoria, Illinois. Tr. at 6. Ms. Robinson works as the vice president of revenue cycle at OSF Healthcare Systems. *Id.* Petitioner's job requires all vaccinations, however she now has vaccination exemptions, specifically for the flu vaccine, given to her by Dr. Burger as a result of her MS diagnosis. *Id.* at 7. Petitioner is the sole provider for her family and is afraid to pursue other opportunities due to her fear that those institutions will require vaccination. *Id.* at 16-17. Petitioner also fears taking any medication as a result of her reaction to the flu vaccine and prefers more holistic treatments. *Id.* at 18-19. Petitioner is in physical therapy for her knees and legs. *Id.* at 19.

Petitioner testified about her symptoms. She stated her arms and leg go numb during meetings, and she needs to go to the bathroom more frequently, especially in the morning. Tr. at 8. Her eyesight is much poorer, and she loses her train of thought during meetings and presentations. *Id.*

Petitioner first noticed tingling in her fingers on her left hand one time when she took a shower around Halloween. Tr. at 9. Her PCP worked in her building and told her that he believed the vaccination "nicked a nerve" and that it would go away. *Id.* Petitioner noticed that on Halloween, October 31, 2011, as she was taking her daughters to see Beauty and the Beast, she had difficulty carrying them and her entire left side felt weak. *Id.* She thought she might have had a stroke. *Id.* at 9-10. Petitioner kept talking with her PCP who then told her he believed it was carpal tunnel syndrome. *Id.* at 10. She underwent an EMG and nerve conduction study, which did not reveal anything. *Id.* Petitioner was unable to remove her Thanksgiving turkey from the oven and could not carry her shopping bags on Black Friday. *Id.* Eventually, Petitioner had an MRI because her arms and legs were numb. *Id.* at 11.

In 2012, Petitioner was diagnosed with optic neuritis. Tr. at 11. Petitioner testified that her eye began hurting when exposed to blue flashing lights. *Id.* Petitioner was admitted to the hospital due to her pain and was started on Solu-Medrol in August and remained hospitalized for three days. *Id.* at 13-14. While hospitalized, Petitioner worked because she had just started a new job and didn't want to give the impression that she had any problems or couldn't perform. *Id.* at 14. Petitioner expressed fears of losing her job because she was a woman in the world of finance. *Id.* at 15. Petitioner had accepted another position at the University of California Hastings but had to withdraw due in part to her inability to be vaccinated. *Id.* at 16. As a sole breadwinner for her family, she feels like she cannot switch jobs due to her concern that a new position will require vaccination. *Id.*

Petitioner stated her condition prevents her from performing everyday activities. Tr. at 17. She states she cannot go into the sun, go to her childrens' games, cross stitch, or read a book. *Id.* She is terrified of putting anything into her body, which includes treatment for her MS. *Id.* at 18.

She is afraid of treatment because she feels like it could still affect her ability to perform her job and reduce the time she spends with her kids. *Id.* Petitioner says her vaccine exemption is reviewed every year by independent physician to see if it is warranted. *Id.* at 230.

B. Mr. Douglas Robinson, Petitioner's husband

Mr. Robinson testified that he lives with Petitioner and their three children in Peoria, Illinois. Tr. at 21. Mr. Robinson stated that Petitioner was diagnosed with multiple sclerosis, and that the doctors indicated her condition would get worse as she gets older. *Id.* As a result of Petitioner's MS diagnosis, Mr. Robinson testified that he has to take on a caretaker role. *Id.* at 24.

Petitioner was diagnosed with optic neuritis but was later diagnosed with MS at the Mayo Clinic. *Id.* at 23. According to Mr. Robinson, Dr. Burger believed Petitioner's condition had to do with the flu vaccine, which is why he gave her a lifetime exemption. *Id.* at 26. Mr. Robinson stated that the doctor at the Mayo Clinic said that what happened to Petitioner was "a perfect storm." *Id.*

IV. Expert Opinions

Petitioner filed one expert report and two supplemental reports from Dr. Steinman. Exs. 13 ("First Steinman Rep."), 43 ("Second Steinman Rep."), and 47 ("Third Steinman Rep."). Dr. Steinman received his medical degree from Harvard University in 1973 and completed his residency at Stanford University in pediatrics and pediatric and adult neurology. Ex. 14 (hereinafter "Steinman CV") at 1. Dr. Steinman is board certified in neurology. *Id.* at 2. He has taught in neurology, pediatrics, and genetics since 1980 and is currently a professor at Stanford University in the departments of Neurology, Pediatrics, and Genetics; he is also the George A. Zimmermann Professor of Neurological Sciences at Stanford University. *Id.* at 1. Dr. Steinman has over 20 patents and has published over 450 peer reviewed papers. *Id.* at 2-37.

Respondent filed an expert report and one supplemental report from Dr. Vartanian. Exs. A ("First Vartanian Rep.") and W ("Second Vartanian Rep.").

Dr. Vartanian received his medical degree from the University of Chicago in 1988 and completed his residency at the Massachusetts General Hospital in neurology. Ex. B (hereinafter "Vartanian CV") at 1-2; Ex. V (hereinafter "Vartanian Second CV") at 1-2. Dr. Vartanian taught at Harvard Medical School from 1992-2009 and is currently an assistant professor of neurology and neuroscience at the Weill Cornell Medical College. Vartanian Second CV at 2. Dr. Vartanian is board certified in neurology, and is active in one research project involving MS. *Id.* at 2, 11. Dr. Vartanian has over 60 peer-reviewed papers and is a peer editor for many publications, some of which include Journal of Cell Biology, Journal of Neuroscience, Brain, Developmental Neuroscience, and Annals of Neurology. *Id.* at 12-21.

A. Expert Reports

1. Dr. Steinman's First Report

In Dr. Steinman's first report, he summarized Petitioner's medical records and opined that if not for the influenza vaccine Petitioner received on October 18, 2011, she "would likely not have developed clinical evidence of multiple sclerosis within 13 days, which ultimately progressed to a fully diagnosed case of MS." First Steinman Rep. at 1.

Regarding the theory of how the flu vaccine caused Petitioner to develop MS, Dr. Steinman opined that the vaccine Ms. Robinson received "contained molecular mimics of three myelin proteins, myelin oligodendroglial glycoprotein (MOG), CNPase, and myelin basic protein (MBP)." First Steinman Rep. at 4. Both MOG and MBP immunity "is capable of eliciting experimental autoimmune encephalomyelitis (EAE) when they are injected into experimental animals." *Id.* Dr. Steinman additionally stated that research on EAE "has led to many FDA approved medicines for MS," such as the discovery of Tysabri, the most potent FDA approved drug for MS. *Id.* Alternatively, Dr. Steinman suggests that the flu vaccine "induces antibodies to gangliosides… Immunity to gangliosides is associated with autoimmune demyelinating disease, including GBS, but also MS." *Id.*

Dr. Steinman also opined about the significance of Ms. Robinson's exemptions given by her treating physician. First Steinman Rep. at 5. The 2011-2012 influenza vaccination had risks of Guillain-Barré syndrome which Dr. Steinman believed Petitioner's treating physician considered when granting Petitioner flu vaccine exemptions. *See id.*

Dr. Steinman identified a sequence of nine amino acids in the hemaglutinnin of the influenza vaccine that he believes cross-reacted with myelin antigens which led to Petitioner's development of MS. *See* First Steinman Rep. at 6-7. Dr. Steinman identified a separate six amino acid sequence that mimics the myelin basic protein in the 2011 influenza vaccine. *See id.* at 7-8. Dr. Steinman argued that the amino acids do not need to be consecutive to affect the myelin basic protein. *See id.* at 9.

Along with the two amino acid sequences that Dr. Steinman identified, he cited to a UPenn/CDC study that show that the H1N1 virus can "elicit immune responses to ganglioside…" *See* First Steinman Rep. at 19-20.

Regarding the timing of onset of Petitioner's symptoms, Dr. Steinman opined that Guillain Barré syndrome is the best surrogate for neuroinflammation induced by influenza vaccines, thus easily fits in the time frame of approximately two weeks. *See* First Steinman Rep. at 20.

2. Dr. Vartanian's First Report

Dr. Vartanian began by stating that the pathophysiology of MS is unknown but through a study done with identical and non-identical twins, we know that 25% of the risk for MS is genetic and 75% environmental. First Vartanian Rep. at 7.

Because the first MRI was performed five months after vaccination, Dr. Vartanian opined that it is difficult to determine when the pathological process of MS began. First Vartanian Rep. at 7-8. Dr. Vartanian did note that Petitioner's spinal fluid showed 12 oligoclonal bands, which according to him, "seems high for an individual at the earliest stages of their disease." First

Vartanian Rep. at 8. He also noted that "we do not have literature that absolutely guides us in this question." *Id.*

Regarding Dr. Steinman's first report, Dr. Vartanian stated that there are more than three cross reactive peptides than the ones cited by Dr. Steinman and "if all of these cross-reactive peptides/proteins/epitopes were relevant then the spectrum of autoimmune disease following influenza infection, as claimed by Dr. Steinman, would be broad." First Vartanian Rep. at 8. Dr. Vartanian reproduced Figure 2 of Markovic-Plese to demonstrate the number of cross-reactive peptides that mimic human myelin sequences. *See id.* at 9-12. One of the peptide sequences identified by Dr. Steinman, the A/California/7/09 (H1N1) sequence, fyknli, has only three shared amino acids with the sequence for the myelin basic protein, ffkniv. *See id.* at 14. These differences "alter relevant protein-protein interactions and immunogenicity." *See id.* In a study monitoring T-cell frequencies before and after vaccine, there was no difference in the frequency of auto-reactive T-cells to myelin basic protein and myelin oligodendrocyte protein. *See id.*

Dr. Vartanian lastly opined that Petitioner's SLIT treatment might be responsible for triggering her MS. First Vartanian Rep. at 16. Dr. Vartanian stated that SLIT treatment

> significantly alters the immune response and one effect it has is on the induction of Micro-RNA-146a (miRNA-146a). Micro RNAs play a key role in gene regulation…. MicroRNA-146a is a well known key proinflammatory post-transcriptional regulator that is up-regulated in MS and thought to play a major role in MS pathogenesis. Although as difficult to prove as the role a vaccination might play in disease initiation, there is as strong a basis for the role of SLIT therapy in induction of MS.

Id. Dr. Vartanian concluded by opining that "there is no reliable, persuasive evidence that influenza vaccination is causative of Ms. Robinson's MS. Rather this is reliable evidence that the more likely cause of her MS is the SLIT therapy." *Id.*

3. Dr. Steinman's Second Report

Dr. Steinman drafted his second expert report in response to Dr. Vartanian's first report. Dr. Steinman addressed Petitioner's T2 lesion found on an MRI in 2012 and indicated there was no credible evidence that it was present before her immunization. Second Steinman Rep. at 1. Dr. Steinman noted that enhancing lesions have a typical duration of two weeks, but Petitioner's was a non-enhancing lesion which according to the literature, would have developed 56 days at the earliest, prior to appearing on the MRI. *See id.* at 1-2. Given this approximation, Petitioner's radiologic findings would have still appeared after the October 18, 2011 vaccination. *See id.* at 2. Dr. Steinman disagreed with Dr. Vartanian's opinion that the lesions occurred prior to the October 18, 2011 vaccination. *See id.* Dr. Steinman additionally opined that while MS susceptibility is associated with over 100 genes, studies involving identical twins show that environmental factors have a "major impact on disease onset and outweigh[] even genetic factors." *See id.* at 2-3.

4. Dr. Vartanian's Second Report

In Dr. Vartanian's second report, he addressed Dr. Steinman's opinion regarding lesions and imaging. He stated, "while defects in established MS lesions are well known, the mechanisms of underlying BBB (blood-brain barrier) dysfunction in MS are not clearly defined." Second Vartanian Rep. at 2. Dr. Vartanian identified studies demonstrating that imaging was highly susceptible to a number of factors, which include water exchange with macromolecules and tissue microarchitecture, cerebral blood flow, and changes in perfusion. *Id.* at 1-4. Dr. Vartanian concluded by stating that the lesions present on Petitioner's MRI "began at least months prior to the date of the MRI since those lesions were non-enhancing and enhancement itself typically lasts for 2-3 weeks." *Id.* at 5.

5. Dr. Steinman's Third Report

Dr. Steinman provided a third report in response to Respondent's filings after the hearing. Third Steinman Rep. at 1. Dr. Steinman reiterated his opinion that there was not preponderant evidence that the lesions on the March 21, 2012 MRI were present before Petitioner's flu vaccination. He further stated his opinion that the lesion developed post-vaccination. *See id.*

B. Expert Testimony

1. Dr. Steinman

Dr. Steinman testified that Petitioner "developed multiple sclerosis about 13 days after she had the […] seasonal influenza vaccine in October of 2011." Tr. at 39. Dr. Steinman opined that there are a variety of genetic and environmental factors can contribute MS, but "one of the important aspects of this case is that the influenza vaccine was given. Her doctors, her treating, board certified doctors attribute the vaccine and the timing as a cause. They have exempted her from further vaccines. And I think far and away it's the best explanation of what caused [Petitioner]'s MS." *Id.* at 40-41.

Regarding Petitioner's oligoclonal bands, Dr. Steinman contested Dr. Vartanian's opinion that "the more bands, the more likely the disease was severe and the more possible that it could have started earlier." Tr. at 41. Dr. Steinman testified that he found no literature to support this proposition. *Id*. at 41-42.

Concerning Petitioner's SLIT therapy, Dr. Steinman first discussed micro RNA-146. Tr. at 44. MiR-146a is a small sequence of ribonucleic acid that has been discovered to be an important regulator of immune function and other functions in the body. *Id.* In the Guo paper cited by Dr. Vartanian, it was found that when miRNA-146a levels are increased, the immune response goes down during SLIT therapy. *Id*. at 44-45. Dr. Steinman testified that miRNA-146a and SLIT therapy are actually suppressing Petitioner's MS rather than initiating it or causing an exacerbation. *Id.* at 46-48.

Dr. Steinman cited the Schonberger and Langmuir studies as a basis for why he believes that onset of MS 13 days after vaccination is reasonable. Tr. at 54.

Dr. Steinman offered testimony on the specifics of his molecular mimicry theory. Tr. at 58-66. The molecular mimicry theory involves the adaptive immune system, B and T cells. *Id.* at 59. In MS cases, a common peptide sequence hffk (histidine, phenylalanine, phenylalanine, and lysine) is recognized by antibodies or T cells. *Id.* at 60. T cells have the ability to recognize sequences that are not identical, thus can attack components of the flu vaccine that Petitioner received. *Id.* at 61-62.

In the Birnbaum paper, the HFFK sequence (or variations like HFYK) was found to stimulate human T cell clones in MS patients. Tr. at 67; *see* Birnbaum, et al., *Deconstructing the Peptide-MHC Specificity of T Cell Recognition*, 157 CELL 1073–87 (2014) (filed as Ex. 18). Dr. Steinman also testified that the Markovic-Plese paper demonstrates how a small change in sequence, like from F to Y, can still cause T cell clones to activate and attack myelin basic protein. *Id.* at 69. *See also* Markovic–Plese, et al., *High level of cross-reactivity in influenza virus hemagglutinin-specific CD4+ T-cell response: Implications for the initiation of autoimmune response in multiple sclerosis*, 169 JOURNAL OF NEUROIMMUNOLOGY 31-38 (2005) (filed as Ex. 26) (hereinafter "Markovic–Plese").

Dr Steinman testified that the only reason a doctor would recommend that an MS patient not receive a flu vaccine is because the vaccine might cause a flare of MS. Tr. at 80. Dr. Steinman stated that he still recommends his MS patients get the yearly flu vaccine. *Id.* at 80-81. However, the Moriabadi paper shows that 33% of patients with relapsing-remitting MS experience an exacerbation of neurologic disease within six weeks of having the flu virus. *See* Moriabadi, et al., *Influenza Vaccination in MS: Absence of T–Cell Response against White Matter Proteins*, 56 NEUROLOGY 938 (2001) (filed as Ex. K) (hereinafter "Moriabadi"); Tr. at 81. Moriabadi showed that 5% of patients who received the flu vaccination experienced a flare. Dr. Steinman described these findings as significant. Tr. at 81-82.

In the case of ganglioside, the Nachamkin paper studied the H1N1 vaccine, and how it can cause an antiganglioside response. Tr. at 85; *see* Nachamkin, et al., *Anti-Ganglioside Antibody Induction by Swine (A/NJ/1976/H1N1) and Other Influenza Vaccines: Insights into Vaccine-Associated Guillain-Barré Syndrome*, 198 JID 226-33 (2008) (filed as Ex. 27). According to Dr. Steinman, this paper demonstrated that an immunity in gangliosides is detectable in individuals with MS. *Id.* Dr. Steinman testified that this is similar to the situation involving c. jejuni and GBS. *Id.* at 85-86.

Dr. Steinman also cited two papers which demonstrate "you needed 5 out of 12 amino acids to be identical to get ADEM (acute disseminated encephalomyelitis)… [which] has many feature of MS, but it's one of the known sequelae of vaccines, including [the] influenza vaccine." Tr. at 101-02. The drug used to treat MS, Copaxone, was discovered from research on EAE (experimental autoimmune encephalitis), which is "the experimental version of ADEM". *Id.* at 102. Thus, Dr. Steinman testified that findings regarding ADEM could be comparable to MS. *See id.* at 102. The Gautam article showed that mice injected with peptides from different viruses caused disease in a substantive percentage of mice, and that the peptides did not need to be perfectly homologous to induce disease. *Id.* at 103-04; Gautam, et al., *A Viral Peptide with Limited Homology to a Self Peptide Can Induce Clinical Signs of Experimental Autoimmune Encephalomyelitis*, 161 J IMMUNOL 60-64 (1998) (filed as Ex. 19).

Dr. Steinman testified that the Epstein Barr virus ("EBV") is a known trigger for MS. Tr. at 107. Petitioner had EBV at some point prior, but there was no evidence it was active. *Id.* at 108. Most adults have been exposed to EBV and don't know about it. *Id.* at 109. Dr. Steinman testified Petitioner may have had EBV as an underlying condition, and the flu vaccine she received aggravated the virus. *Id.* at 109-10.

Dr. Steinman disagreed with Dr. Vartanian that Petitioner's MS lesions predated her flu vaccination. He testified that Petitioner's enhancing lesion could have developed within days of the onset of her symptoms "which would have been more than a week after the influenza shot." Tr. at 257.

2. Dr. Vartanian

Dr. Vartanian described what constitutes a non-enhancing lesion. Tr. at 147. In MRI imaging, patients are injected with a gadolinium dye, which will leak into the brain if there is an opening of the blood-brain barrier. *Id.* at 148. In a normal person or a person with MS who is not having a flare, the dye remains in the blood. *Id.* In Petitioner's case, the non-enhancing lesion demonstrated there was a robust breakdown of the blood-brain barrier and inflammation due to the contrast or dye. *Id.* at 149. Dr. Vartanian cited to a study performed by John Prineas, where patients who had died with a diagnosis of MS were discovered to have breakdown of the blood-brain barrier, but no infiltrating lymphocytes were found.[5] *Id.* at 149-50.

Dr. Vartanian testified that the lesion in Petitioner's brain from the March 2012 MRI was unlikely to have caused the tingling and numbness in her arm. *Id.* at 206-07. It is more likely that Petitioner had a lesion in her spinal cord that would have produced her symptoms. *Id.* at 207. The later discovered C4 lesion in the August 2012 MRI would better explain Petitioner's symptoms. *Id.* at 209. Dr. Vartanian stated that if a lesion is in a neurologically obvious area then symptoms could start immediately. *Id.* at 217.

Dr. Vartanian testified that Petitioner's description of her hand tingling during a shower is consistent with MS. Tr. at 153. In a heated environment, symptoms may occur because "focal regions of demyelination function less efficiently at slightly elevated body temperatures." *Id.* Dr. Vartanian opined that this was the first symptom of Petitioner's demyelinating condition. *Id.* Dr. Vartanian also testified that in his opinion, Petitioner had a pre-existing lesion that became active or exacerbated in the shower, with the increase of body temperature. *Id.* at 211-12.

Dr. Vartanian discussed Petitioner's twelve oligoclonal bands. Tr. at 154-59. He agreed with Dr. Steinman that there is no literature regarding oligoclonal band development correlating with length of disease, but it is his opinion that Petitioner "probably had MS for years" and that by the time symptoms reveal themselves, most patients have multiple MRI lesions that are non-enhancing. *Id.* at 154-55. Dr. Vartanian testified that the formation of a lesion is the beginning of MS. *Id.* at 155-56. Because there was no imaging obtained when Petitioner first exhibited

[5] While this study was discussed, it was not filed into the record.

symptoms in October 2011, we can never know when Petitioner's MS began. *Id.* at 156. Oligoclonal bands occur in the cerebral spinal fluid (CSF) when B cells are exposed to antigens in the periphery and make immunoglobulins. *Id.* at 157. This build up "happens over time." *Id.*

Regarding EBV, Dr. Vartanian testified that there is a statistical association between MS and EBV. However, because nearly 95% of the population is exposed to EBV, it "doesn't mean you are going to have MS." Tr. at 159-60. Dr. Vartanian noted that obesity or a high body mass index, being a woman, and being of northern European descent also increase the risk of developing MS. *Id.* at 160.

Dr. Vartanian next opined about Petitioner's SLIT therapy. Tr. at 161-64. Dr. Vartanian agreed with Dr. Steinman that SLIT therapy is typically thought of as a down regulator of immunity. *Id.* at 161. However, the package insert for SLIT therapy includes a risk of anaphylaxis, severe aggravation of asthma and immune conditions, such as eosinophilic esophagitis. *Id.* at 162. Thus, the effects of SLIT therapy on Petitioner are actually unknown. *Id.* However, Dr. Vartanian eventually opined that Petitioner's MS was naturally and spontaneous occurring and was not related to anything else, to include SLIT. *Id.* at 222-23. His conclusion at the end of his first report, according to him, was poorly worded and he meant to state that the influenza vaccine and SLIT were equally likely to have caused Petitioner's MS. *Id.* at 223.

Dr. Vartanian also discussed the Markovic-Plese paper. Tr. at 166-82. According to Dr. Vartanian, this paper was written in an era during which researchers were developing a peptide library. *Id.* at 166. Researchers had discovered ways to synthesize thousands of peptides and test them, creating a "combinatorial library". *Id.* at 167. Through this research, peptide substitutes could be identified and computer algorithms could be used "to assign values to each position for each peptide in terms of its ability to stimulate that clone." *Id.* at 170. The tables in the Markovic-Plese paper identify the amino acid substitution "that gave the best score in this combinatorial chemistry experiment". *Id.* at 171. Table 2 of the paper shows that there are many pathogens that also have similar structures which would seem to indicate it could also stimulate activity. *Id.* at 173.

Dr. Vartanian discussed the Moriabadi paper. Tr. at 183-87. Dr. Vartanian noted that the study was flawed because "it is well known in MS clinical trials that questionnaires and surveys are completely unreliable." *Id.* at 184. Dr. Vartanian also testified about the Metze paper, where MS patients on immunomodulatory immunosuppressive therapies reported no adverse events from the flu vaccine. *Id.* at 187; Metze, et al, *Immunogenicity and predictors of response to a single dose trivalent seasonal influenza vaccine in multiple sclerosis patients receiving disease-modifying therapies*, CNS 25 NEUROSCIENCE & THERAPEUTICS, 245-54 (2010) (filed as Ex. O).

Dr. Vartanian testified that in his opinion, Petitioner's MS lesions predated her flu vaccination. He discussed lesion evolution and testified that there is a process that takes place before an MS lesion will enhance on MRI, stating "there are focal changes at that region of interest anywhere from a month to six months prior." Tr. at 152. Dr. Vartanian cited to several studies in support of his opinion.

Regarding Petitioner's flu vaccine exemption, Dr. Vartanian opined that assessing other physician's reasoning is difficult but it could be that a physician believes there is a causal relationship between the flu vaccine and Petitioner's MS, but it could also be possible that the physician recognizes Petitioner's fear of the vaccine and "doesn't want to put her through that." Tr. at 190-91. Dr. Vartanian confirmed that he always recommends vaccination to his MS patients. *Id.* at 190.

V. Applicable Law

A. Petitioner's Burden in Vaccine Program Cases

Under the Vaccine Act, a petitioner may prevail in one of two ways. First, a petitioner may demonstrate that she suffered a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the time period provided in the Table. § 11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed in the Vaccine Injury Table, a petitioner may demonstrate that he suffered an "off-Table" injury. § 11(c)(1)(C)(ii).

For both Table and non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. § 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [she] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010); *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Hum. Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Hum. Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Hum. Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioner establish by preponderant evidence that the vaccination he received caused his injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278.

Under the first prong of *Althen*, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d

543, 548 (Fed. Cir. 1994). Proof that the proffered medical theory is reasonable, plausible, or possible does not satisfy a petitioner's burden. *Boatmon v. Sec'y of Health & Hum. Servs.*, 941 F.3d 1351, 1359-60 (Fed. Cir. Nov. 7, 2019).

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). However, special masters are "entitled to require some indicia of reliability to support the assertion of the expert witness." *Boatmon*, 941 F.3d at 1360, *quoting Moberly*, 592 F.3d at 1324. Special Masters, despite their expertise, are not empowered by statute to conclusively resolve what are complex scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu*, 569 F.3d at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Hum. Servs.*, 121 Fed. Cl. 230, 245 (2015), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017); *see also Hock v. Sec'y of Health & Hum. Servs*., No. 17-168V, 2020 U.S. Claims LEXIS 2202 at *52 (Fed. Cl. Spec. Mstr. Sept. 30, 2020).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Hum. Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Hum. Servs*., 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing … that mandates that the testimony of a treating physician is sacrosanct -- that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record -- including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Hum. Servs*., 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Hum. Servs*., No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Hum. Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 F. App'x 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Hum. Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. Law Governing Analysis of Fact Evidence

The process for making factual determinations in Vaccine Program cases begins with analyzing the medical records, which are required to be filed with the petition. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Hum. Servs.*, 3 F.3d 413, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records created contemporaneously with the events they describe are presumed to be accurate and "complete" such that they present all relevant information on a patient's health problems. *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Hum. Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical records was rational and consistent with applicable law"), *aff'd*, *Rickett v. Sec'y of Health & Hum. Servs.*, 468 F. App'x 952 (Fed. Cir. 2011) (non-precedential opinion). This presumption is based on the linked proposition that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Hum. Servs.*, No. 11-685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013), *mot. for review den'd* (Fed. Cl. Feb. 11, 2019), *vacated on other grounds*, 809 Fed. Appx. 843 (Fed. Cir. 2020); *Cucuras v. Sec'y of Health & Hum. Servs.*, 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d at 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms.").

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Hum. Servs.*, No. 03-1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony -- especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; see also *Murphy v. Sec'y of Health & Hum. Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992), (citing *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Hum. Servs.*, 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Hum. Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Hum. Servs.*, No. 90-2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *LaLonde v. Sec'y of Health & Hum. Servs.*, 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. Analysis of Expert Testimony

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of her claim. *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993). *See Cedillo v. Sec'y of Health & Hum. Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (*citing Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique

has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora. *Daubert* factors are employed by judges to exclude evidence that is unreliable and potentially confusing to a jury. In Vaccine Program cases, these factors are used in the weighing of the reliability of scientific evidence. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate persuasiveness and reliability of expert testimony has routinely been upheld. *See*, e.g., *Snyder*, 88 Fed. Cl. at 743. In this matter, (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts of his own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)). A "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly*, 592 F.3d at 1324. Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Id.* at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Hum. Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

D. Consideration of Medical Literature

Although this decision discusses some but not all of the medical literature in detail, I reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Hum. Servs.*, 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

VI. Analysis

Because Petitioner does not allege an injury listed on the Vaccine Injury Table, her claim is classified as "off-Table." As noted above, to prevail on an "off-Table" claim, Petitioner must prove by preponderant evidence that she suffered an injury and that this injury was caused by the vaccination at issue. *See Capizzano*, 440 F.3d at 1320.

A. MS Generally

MS is an autoimmune demyelinating disorder of the central nervous system whose cause and pathogenesis are incompletely understood. Steinman & Zamvil, *How to Successfully Apply Animal Studies in Experimental Allergic Encephalomyelitis to Research on Multiple Sclerosis*, 60 ANN NEUROL 12-21 (2006) (filed as Ex. 33) (hereinafter "Steinman & Zamvil"). Although genetic factors have been associated with MS, "[a] genetic basis for MS is clearly only part of the story because concordance in identical twins is less than even 50%." *Id.* at 12. MS is likely due to both genetic and environmental factors. A. Sadovnick, *Familial recurrence risks and inheritance of multiple sclerosis*, 6 CURRENT SCIENCE ISSN 189-94 (1993) (filed as Ex. 46). "[S]moking, low vitamin D levels, infection with Epstein Barr virus, and obesity increase [the] risk of MS." First Vartanian Rep. at 7.

MS is characterized by the "formation of plaques located primarily in the white matter." Tartaglia et al., *Choline is increased in pre-lesional normal appearing white matter in multiple sclerosis*, 249 J NEUROL 1382-90 (2002) (filed as Ex. BB). These lesions appear as hypersensitivities on MRI. *Id.* at 1382.

When an MRI is accomplished, MS lesions can appear as enhancing or non-enhancing. Before a patient has an MRI with contrast, they are injected intravenously with a contrast dye called gadolinium. In a healthy person, or in an MS patient not having a flare, that dye should remain in the bloodstream. However, if an MS patient is symptomatic, the gadolinium will leak into the brain through an opening in the blood-brain barrier and will show as an enhancing image on MRI. *See* Tr. at 147-48. "[Gadolinium] enhancement is the radiologic sign of an active lesion as it signifies breakdown of the blood-brain barrier." Wiggerman et al. *Magnetic resonance frequency shifts during acute MS lesion formation*, 81 NEUROLOGY 211-18 (2013) (filed as Ex. Y) (hereinafter "Wiggerman"). According to Dr. Vartanian, contrast enhancement is synonymous with new symptoms and further, the formation of a lesion constitutes the beginning of disease. *Id.* at 155-56, 211. Dr. Vartanian further testified that three factors cause lesions to be symptomatic 1) location; 2) size; and 3) degree of inflammation. Tr. at 205-06.

B. Did Petitioner's Lesions Pre-Date her Flu Vaccination?

An important question in this case is when Petitioner's lesions formed. Petitioner contends they formed after her flu vaccination; Respondent disputes this point and takes the position that Petitioner's lesions formed prior to vaccination. Resolution of this issue is critical, because if Petitioner's lesions predated her vaccination, the flu shot cannot have caused her condition.

This case differs from other cases in the Program that have addressed whether flu vaccine can cause MS in that Petitioner did not have an MRI until approximately five months after she developed her first symptoms. Because of that, it is difficult to establish when Petitioner's lesions formed. She had her first MRI on March 21, 2012. Ex. 3 at 47-48. This MRI depicted a non-enhancing lesion in the brain. Dr. Vartanian specifically testified that this lesion was most likely not responsible for Petitioner's first MS symptoms (hand tingling) that developed on October 31, 2011. Tr. at 153. Dr. Vartanian testified that this particular lesion was at least four weeks old, but he was unable to say when it formed because it was non contrast-enhancing. *Id.* at 204.

Petitioner had a second MRI of the brain on August 2, 2012. Ex. 3 at 50-51. The MRI revealed "minimal thickening and enhancement of the left optic nerve." Ex. 3 at 51. This MRI also revealed the "redemonstration of minimal abnormal signal in the deep white matter of the brain" along with a new right periventricular lesion. *Id.* at 50-51. Both lesions were notable for faint enhancement. *Id.* at 51.

An MRI of the cervical spine performed on August 10, 2012 revealed a tiny lesion at cervical level 4, which, according to Dr. Vartanian, was probably the lesion responsible for her initial symptoms. Ex. 3 at 24; Tr. at 153-54. At the time of the imaging, this C4 lesion was also non-enhancing. *Id.* at 225. *See* Ex. 3 at 24 (indicating, "A tiny T2 hyperintense focus noted in the spinal cord on the left side at the level of C4 may be artifactual. … No abnormal enhancement is noted within the cervical cord after contrast injection.").

Dr. Vartanian testified that Petitioner's onset of symptoms on October 31st was "synonymous with a contrast-enhancing lesion." Tr. at 216. In other words, though not documented on MRI, Petitioner likely experienced her initial symptoms of MS as a result of a contrast enhancing lesion on her spinal cord. Based on this, Respondent contends that Petitioner's lesion pre-dated her flu vaccine. Petitioner argues that the evidence supports onset of MS after vaccination.

With respect to this issue, Dr. Vartanian discussed lesion evolution, and testified that there is a process that takes place before an MS lesion will enhance on MRI. Tr. at 150. He testified that "there are focal changes at that region of interest anywhere from a month to six months prior." *Id.* at 152. Dr. Vartanian later qualified that statement some and opined that "there is evidence at that focal region of blood-brain barrier opening and tissue injury that predates contrast enhancement by weeks to months." *Id.* at 211.

In support of his opinion that a sub-clinical lesion forms before symptom onset, Dr. Vartanian cited to several studies. One such study was Absinta. *See* Absinta et al., *Direct MRI detection of impending plaque development in multiple sclerosis*, NEUROL NEUROIMMUNOL NEUROINFLAMM (2015) (filed as Ex. X) (hereinafter "Absinta"). Tr. at 214-15. Absinta looked at 308 scans from 29 patients over a four-year period for the presence of contrast enhancement. *Id.* at 253-54. Of the 308 scans in the study, 87 had a total of 162 contrast-enhancing lesions. *Id.* at 254. Further, 121 of those 162 contrast-enhancing lesions had a prior MRI within a two-month period where 26 showed signal changes that preceded enhancement. *Id.* at 254. Dr. Vartanian testified that "in five of the cases, five contrast-enhancing lesions in five different patients, they

identified linear enhancement within that venule in the absence of any brain or parenchymal enhancement. And this was observed 8 to 31 days prior to parenchymal enhancement." *Id.* at 255.

The Absinta article found that "In approximately 15% of new active lesions, parenchymal enhancement has directly visible antecedent MRI changes that, in cases where the T2*-weighted sequence was available for investigation, are centered on the central vein." Absinta at 2. I note that this article does not suggest that antecedent MRI changes are present in all or even the majority of active lesions.

Dr. Steinman testified that Absinta did not preclude the flu vaccine as the cause of Petitioner's symptoms in this case. He testified that the study indicated that "in some cases small parenchymal, that means within the brain, signal changes on T2 flare or T2 weighted scans around the vein were detected days to weeks before enhancement." Tr. at 257. Dr. Steinman additionally testified as follows:

> Then he also had some evidence of blood-brain barrier breakdown where there was some enhancement as early as eight days before and other scans as long as 31 days before. So if you look at the actual data in Absinta and Reich, there is no reason to discount that in the 13 days … after the immunization that they would have seen with these wonderful tools available at the NIH the beginning of something. But there is no reason to say that by any stretch of the imagination or any stretch of looking at this literature that it had to have begun before the vaccine.

Tr. at 234.

Dr. Steinman's position at hearing was that Petitioner's enhancing lesion could have developed within days of the onset of her symptoms "which would have been more than a week after the influenza shot." Tr. at 257.

Respondent filed the Wiggerman article in support of his position that MS lesions begin to develop before they appear on MRI. In this study, patients with relapsing-remitting MS were scanned on a monthly basis for six months. The study found an increase in magnetic resonance frequency one month before and one month after gadolinium enhancement.[6] Wiggerman at 213. However, some of the findings also seem to support Petitioner's position. The authors further stated that "[u]p to 3 months before lesion appearance, the frequency in areas of future [gadolinium] enhancement was not detectably different from the frequency in normal-appearing white matter." *Id.* at 211. Further, the Wiggerman article noted that "One finding of the present study was that MR frequency increased rapidly at the time of enhancement, relative to one or more months prior." *Id.* at 215. This last point seems to support Petitioner's position that the timing of

[6] However, the article noted that some of the lesions "exhibited a behavior quite different from the general trend … such as an increase in frequency more than 3 months before Gd enhancement, a decrease in frequency during the months before enhancement, or no change in frequency during the first 2 months after enhancement." This demonstrates that not all the lesions behaved the same way, although a discussion of each lesion was not provided. *Id.* at 213.

contrast enhancement may occur at the time of lesion development and not weeks to months preceding this observation on MRI.

The experts also discussed the Cotton study, which calculated the mean and median duration of enhancement in lesions of 26 relapsing-remitting MS patients. Cotton et al., *MRI contrast uptake in new lesions in relapsing-remitting MS followed at weekly intervals*, 60 NEUROLOGY 640-46 (2003) (filed as Ex. 44) (hereinafter "Cotton"). Cotton found that the mean duration of enhancement was 3.07 weeks while the median duration was two weeks. Cotton at 640. Figure 1 of Cotton demonstrates that 60 percent of contrast enhancing lesions were present for two weeks or less; 30 percent were present for one week or less. *Id.* at 642; Tr. at 238.

Based on the testimony of the experts and the literature filed in this case, I do not find there is preponderant evidence that Petitioner's MS lesions predated her vaccination. After evaluating each of the studies, Dr. Vartanian opined as follows: "This suggests that the lesions present on Ms. Robinson's MRI began at least months prior to the date of the MRI since those lesions were non-enhancing and enhancement itself typically lasts for 2-3 weeks." Third Vartanian Rep. at 5. Even if Dr. Vartanian's conclusion is correct, "months prior" to Petitioner's March 2012 MRI is still most likely after her flu vaccine in October 2011. Although Dr. Vartanian did testify at hearing that Petitioner's onset of symptoms on October 31st was likely "synonymous with a contrast-enhancing lesion" (Tr. at 216), Absinta shows there may have been a breakdown in the blood brain barrier between eight and 31 days before contrast enhancement in *some* lesions (15%). Presumably this breakdown in the blood brain barrier was not seen in the other 85%. This issue is a close call. Certainly, Dr. Vartanian has made a good case for the fact that a certain percentage of lesions begin forming before contrast enhancement on MRI. However, based on the specific facts of this case, where an MRI was not performed until five months after symptom onset, it is difficult to apply these studies to this case in a meaningful way. Ultimately, I find that Petitioner's lesion more likely than not formed after her vaccination.

C. *Althen* Prongs

I will address the *Althen* prongs in their order of significance based on the facts of this case.

1. *Althen* Prong One

In the context of the Program, "to establish causation, the standard of proof is preponderance of evidence, not scientific certainty." *Langland v. Sec'y of Health & Hum. Servs.*, 109 Fed. Cl. 421, 441 (2013). Petitioner's burden under *Althen*'s first prong is to provide a medical theory causally connecting the vaccination and the injury. *Id.* This theory must be sound and reliable. *Boatmon*, 941 F.3d at 1359.

At the outset, I note other cases in the Vaccine Program have addressed the issue of whether the flu vaccine (or other vaccines) can cause or significantly aggravate MS. *See, e.g., Hitt v. Sec'y of Health & Hum. Servs.*, No. 15-1283V, 2020 WL 831822 (Fed. Cl. Spec. Mstr. Jan. 24, 2020)

(finding the flu vaccine caused the petitioner's MS);[7] *P.M. v. Sec'y of Health & Hum. Servs.*, No. 16-949V, 2019 WL 5608859 (Fed. Cl. Spec. Mstr. Oct. 31, 2019) (finding that the flu vaccine did not significantly aggravate petitioner's preexisting MS); *but see Quackenbush-Baker v. Sec'y of Health & Hum. Servs.*, No. 14-1000V, 2018 WL 1704523 (Fed. Cl. Spec. Mstr. Mar. 14, 2018) (finding that the flu vaccine significantly aggravated the petitioner's preexisting MS); *W.C. v. Sec'y of Health & Hum. Servs.*, 100 Fed. Cl. 440 (2011) (upholding special master's determination that flu vaccine did not significantly aggravate preexisting MS), *aff'd,* 704 F.3d 1352 (Fed. Cir. 2013), *and Doe29 v. Sec'y of Health & Hum. Servs.*, 2009 WL 180078 (Fed. Cl. Spec. Mstr. Jan. 21, 2009) (finding that the Hepatitis B vaccine caused petitioners to develop MS); *Doe23 v. Sec'y of Health & Hum. Servs.*, 2008 WL 4865974 (Fed. Cl. Spec. Mstr. Oct. 31, 2008); *Pecorella v. Sec'y of Health & Hum. Servs.*, No. 04–1781V, 2008 WL 4447607 (Fed. Cl. Spec. Mstr. Sep. 17, 2008) (same).

Petitioner presented a theory that the flu vaccine caused her MS by means of molecular mimicry. The molecular mimicry theory hypothesizes that a foreign antigen resembles an antigen produced by the body. This similarity results in T cells attacking host body tissue. Steinman & Zamvil at 109. Molecular mimicry is a well-established theory in the Vaccine Program and has been persuasively linked to different immune-mediated conditions. For example, special masters have recognized molecular mimicry as the method by which streptococcus bacteria can develop into Sydenham's chorea and that c. jejuni infection can cause Guillain-Barré syndrome (GBS). *W.C. v. Sec'y of Health & Hum. Servs.*, No. 07-456V, 2011 WL 4537877, at *11 (Fed. Cl. Spec. Mstr. Feb. 22, 2011), *mot. for rev. denied in relevant part,* 100 Fed. Cl. 440, 451-53 (2011), *aff'd,* 704 F.3d 1352 (Fed. Cir. 2013); *Isaac v. Sec'y of Health & Hum. Servs.*, No. 08-601V, 2012 WL 3609993, at *4 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for rev. denied,* 108 Fed. Cl. 743 (2013), *aff'd without op.*, 540 Fed. App'x 999 (Fed Cir. 2013).

In this case, Dr. Steinman testified that "it was that cross-reaction in her influenza shot with those myelin constituents that triggered her clinical appearance of MS 13 days later." Tr. at 87. Specifically, Petitioner's flu vaccine resulted in autoreactive T-cells; these T-cells were cross-reactive with myelin antigens and resulted in an autoimmune injury to myelin. Dr. Steinman based his theory on several studies.

Dr. Steinman discussed the Wucherpfennig studies. *See* Wucherpfennig, et al., *Recognition of the Immunodominant Myelin Basic Protein Peptide by Autoantibodies and HLA-DR2-restricted T Cell Clones from Multiple Sclerosis Patients*, 100 J CLIN INVEST 5, 1114-22 (1997) (filed as Ex. 34) (hereinafter "Wucherpfennig1"); KW Wucherpfennig & JL Strominger, *Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein*. 80 CELL 5, 695-705 (1995) (filed as Ex. 36) (hereinafter "Wucherpfennig2"). Wucherpfennig1 tested peptides containing protein sequences that share a similar structure with myelin basic protein to see if they stimulated the production of T-cells. Wucherpfennig1 at 1114. The results showed that the influenza A peptide sequence (among others) stimulated T-cells. Dr. Steinman indicated that this study supported his molecular mimicry theory with respect to the flu vaccine and myelin basic protein. He testified that "antibodies from autopsy MS brains ... cross-

[7] I note that the Respondent's expert in this particular case testified that the flu vaccine can cause MS. *Hitt*, 2020 WL 831822, at *10.

react, they can bind myelin basic protein, and the same antibody can bind influenza virus." Tr. at 106. The Wucherpfennig studies demonstrate that T cells isolated from the blood of patients with multiple sclerosis share a peptide sequence with the flu virus. These studies provide an example of molecular mimicry with influenza strains contained in the same vaccine that Petitioner received.

Dr. Steinman also testified at hearing about the Markovic–Plese study. That study found that cloned human T-cells which reacted to an influenza virus hemagluttinin peptide also reacted to three peptides derived from human myelin proteins. Markovic–Plese also found significant homology between flu-hemagluttinin and those myelin proteins. Dr. Steinman noted the importance of Markovic–Plese's research, in part because it was on conducted on T-cells and myelin proteins derived from a human subject diagnosed with MS. He believed that the study supported his theory that the flu vaccine can prompt an autoimmune response that causes MS. Dr. Steinman testified, "a human clone from an MS patient taken after somebody with an influenza infection triggers a response that cross-reacts with myelin proteins that are known to be involved in MS." Tr. at 99.

Dr. Steinman testified that the findings in the Markovic–Plese study are important with respect to Petitioner's case. Markovic–Plese's research involved a flu-hemagluttinin peptide sequence YVKQNTLKL. Markovic–Plese at 3. Dr. Steinman reported that this sequence contains an identical nine amino acid sequence to the Perth strain of the 2011/2012 vaccine that Petitioner received. Tr. at 138-39. Dr. Steinman testified that this indicates that the 2011/2012 flu vaccine can cause the same cross-reactivity to myelin that was observed in Markovic–Plese.

> And that's what these studies show, that in a person with MS, these myelin reactive cells are actually -- you can find them in the lesion. You can find the myelin reactive cells. You can find the myelin reactive antibodies. And we actually took them out of MS brains from 12 patients in the Wucherpfennig paper.

Id. at 71. Dr. Steinman further opined that "there is enough data in the Markovic paper and the other papers that show that influenza vaccine and influenza infection can stir up a lot of cross-reactive immunity to myelin proteins." *Id.* at 138.

Dr. Vartanian testified at hearing about Markovic–Plese. *See* Tr. at 166-79. He opined, "there are many human mimics other than the myelin mimics. If all of these cross-reactive peptides/proteins/epitopes were relevant, then the spectrum of autoimmune disease following influenza infection … would be broad." First Vartanian Rep. at 8.

Although Dr. Steinman conceded that there are no epidemiological studies linking flu vaccine to MS, he testified that a paper by McNicholas and Chataway from the National Neurology Hospital in London helps support Petitioner's theory. This paper was not filed as an exhibit in this case, but instead was cited in several of Respondent's exhibits.[8] *See e.g.*, Mailand, et al., *Vaccines and multiple sclerosis: a systematic review*, 264 J NEUROL 1035-50, fn. 38 (2017) (filed as Ex. Q)

[8] I note that I did not independently review this article, but instead relied upon Dr. Steinman's testimony concerning the article.

(hereinafter "Mailand");[9] Mahmud, et al., *Registry Cohort Study to Determine Risk for Multiple Sclerosis after Vaccination for Pandemic Influenza A(H1N1) with Arepanrix, Manitoba, Canada*, 24 EMERGING INFECTIOUS DISEASES 7, 1267-74, fn. 33, (2018) (filed as Ex. P) (hereinafter "Mahmud"). According to Dr. Steinman, the McNicholas and Chataway study demonstrated that "in a cohort of 20-some-odd patients over 50 percent of them had a flare after getting either an H1N1 vaccine or an H1N1 vaccine plus a seasonal flu vaccine." Tr. at 243. He further testified that "[e]ighteen patients in their clinic were vaccinated, and in their flowchart with H1N1 vaccine alone, six of seven relapsed within three weeks, and four of eight that got the H1N1 and a seasonal flu relapsed within three weeks." *Id.* Dr. Steinman conceded that these results were obtained in one out of 14 studies. *Id.* at 244. The other 13 did not find an association between flu vaccine and MS. He stated, "I can't explain why very good neurologists at the National Neurology Hospital in London had those kind of data." *Id.* Dr. Steinman described the study as "rather strong evidence that ... something is going on there with an influenza vaccine in their eyes in their clinic." *Id.*

Both Petitioner and Respondent discussed the Moriabadi article. MS patients were immunized with the influenza vaccine. The researchers then tested their blood two and four weeks after vaccination to see if they developed an increased number of T-cells that reacted with myelin basic protein. The study found "no difference in the frequency of autoreactive T-cells to myelin basic protein and myelin oligodendrocyte protein as well is to control proteins such as tetanus toxoid." First Vartanian Rep. at 14.

The Moriabadi article cited to a reference which found that five percent of 180 MS patients (a total of nine patients) experienced an exacerbation in neurologic disease after influenza vaccination. Moriabadi at 938; Tr. at 56. According to Dr. Steinman, this study suggests that "there must be something going on between influenza vaccine … and MS." *Id.* at 118. Dr. Vartanian discussed this reference in Moriabadi. He described it as "a retrospective analysis that used questionnaires in a German database to find people who had influenza or influenza vaccinations and ask them if they had had an exacerbation [of MS]." *Id.* at 184. Dr. Vartanian discounted these results as unreliable due to the fact that they were derived from questionnaires. *Id.*

The majority of studies conclude that there is no increased risk of developing MS or exacerbating MS after flu vaccination. Epidemiologic evidence is relevant with respect to *Althen* prong one. *See, e.g., D'Tiole v. Sec'y of Health & Hum. Servs.,* 2016 U.S. Claims LEXIS 2003 (Fed. Cl. Spec. Mstr. Nov. 28, 2016), *mot. for review den'd*, 132 Fed. Cl. 421 (2017), *aff'd*; *Blackburn v. Sec'y of Health & Hum. Servs.*, No. 10–410V, 2015 WL 425935, at *28–30 (Fed. Cl. Spec. Mstr. Jan. 9, 2015). However, this type of evidence is not required in order for a petitioner to establish that a vaccine can cause an injury. A vaccine injury is a rare event that cannot be disproved because a vaccinee did not experience a response consistent with that of the general population. *See Harris v. Sec'y of Health & Hum. Servs.*, No. 10–322V, 2014 WL 3159377, at *11 (Fed. Cl. Spec. Mstr. June 10, 2014) (finding that epidemiologic studies cannot absolutely

[9] Respondent also cited to Mailand as evidence that there is not an association between vaccination and MS. Mailand is a literature review which discussed six studies regarding the risk of developing MS after either H1N1 or seasonal influenza vaccination, and 14 studies about the risk of MS relapse after influenza vaccination.

refute causal connections, because it is possible that a larger study could always detect an increased risk), *mot. for review dismissed*, 2015 U.S. App. LEXIS 7921 (Fed. Cir. 2015).

It is settled that "close calls" as to the causal link between a vaccine and the injury asserted by a petitioner should be resolved in favor of the petitioner. *Knudsen by Knudsen*, 35 F.3d at 549. While the majority of studies conclude there is no association between flu vaccine and MS, two studies support Petitioner's position. These studies, combined with the molecular mimicry theory articulated by Dr. Steinman constitute sufficiently reliable evidence that the flu vaccine can cause MS.

2. *Althen* Prong Three

The timing prong contains two parts. First, a petitioner must establish the "timeframe for which it is medically acceptable to infer causation" and second, she must demonstrate that the onset of the disease occurred in this period. *Shapiro v. Sec'y of Health & Hum. Servs.*, 101 Fed. Cl. 532, 542-43 (2011), *recons. denied after remand on other grounds*, 105 Fed. Cl. 353 (2012), *aff'd without op.,* 503 F. App'x 952 (Fed. Cir. 2013).

The parties do not dispute the fact that Petitioner first began to experience symptoms of MS (hand tingling) 13 days after she received her flu vaccine. Tr. at 229.

Dr. Steinman conceded that there are no studies regarding the appropriate onset interval for MS after flu vaccine that are directly applicable to this case. He opined that the Langmuir study is analogous to this case and supports onset of MS 13 days after vaccination. Tr. at 48-52; Ex. 25. Langmuir et al., *An Epidemiologic and Clinical Evaluation of Guillain-Barré Syndrome Reported in Association with the Administration of Swine Influenza Vaccines*, 119 AM J EPIDEMIOL 841-79 (1984) (filed as Ex. 25) (hereinafter "Langmuir"). Langmuir found an increased risk of developing GBS within six weeks of receipt of the H1N1 vaccination.

Dr. Steinman also cited to the experimental allergic encephalomyelitis ("EAE", the animal model of multiple sclerosis) and testified that this further supports onset of MS 13 days after flu vaccination. *See* Steinman & Zamvil at 13. He stated, "If I inject an experimental animal with myelin, for instance, about 13 days later, it can get paralyzed with something that looks like MS." Tr. at 52-53.

Finally, Dr. Steinman referenced Moriabani's reference to a study which found that 5% of the 180 MS patients studied experienced an exacerbation of neurologic disease within six weeks following influenza vaccination. Moriabadi at 938. He testified that this finding supports onset of MS 13 days after flu vaccine. Tr. at 56-57.

Ultimately, Dr. Steinman concluded that 13 days is a medically appropriate onset interval between vaccination and onset of MS. First Steinman Rep. at 21; Tr. at 54.

I will note that in the Hepatitis B-demyelinating diseases omnibus proceedings, former Special Master Millman found that onset of demyelinating diseases of the peripheral *and* central

nervous systems can occur between three days and two months after vaccination. *See e.g.*, *Pecorella* 2008 WL 4447607.

I find that 13 days is a medically acceptable timeframe to infer causation. Although Langmuir involves the onset of GBS after swine flu vaccine, I find Dr. Steinman provided persuasive testimony on the applicability of that study to the present case. The EAE model of ADEM/MS and the finding from the Moriabani article further support this position. Petitioner has satisfied the third *Althen* prong.

3. *Althen* Prong Two

Under *Althen's* second prong, a petitioner must "prove a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. The sequence of cause and effect must be "'logical' and legally probable, not medically or scientifically certain." *Id.* A petitioner is not required to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." *Id.* (omitting internal citations). *Capizzano v. Sec'y of Health & Hum. Servs*., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, circumstantial evidence and reliable medical opinions may be sufficient to satisfy the second *Althen* prong.

At the outset, I will note that because Petitioner has established that flu vaccine can cause MS and that the timing prong has been met this helps establish that she has also demonstrated that vaccination was a but-for cause of her condition. The Federal Circuit has provided guidance with respect to this issue.

> Evidence demonstrating petitioner's injury occurred within a medically acceptable time frame bolsters a link between the injury alleged and the vaccination at issue under the "but-for" prong of the causation analysis. *See Capizzano*, 440 F.3d at 1326 (finding medical opinions that explain how a vaccine can cause the injury alleged coupled with evidence demonstrating a close temporal relationship "are quite probative" in proving actual causation).

Pafford, 451 F.3d at 1358. *See also Contreras* (finding that there is a "logical overlap between the three *Althen* prongs, and that evidence that goes to one prong may also be probative for another prong"). 107 Fed. Cl. at 295.

a. *Petitioner's Treating Physician*

In weighing evidence, special masters are expected to consider the views of treating doctors. *Cappizano*, 440 F.3d at 1326. The views of treating doctors about the appropriate diagnosis are often persuasive because the doctors have direct experience with the patient whom they are diagnosing. *See McCulloch v. Sec'y of Health & Hum. Servs.*, No. 09-293V, 2015 WL 3640610, at *20 (Fed. Cl. Spec. Mstr. May 22, 2015).

On October 3, 2012, Petitioner's treating neurologist, Dr. Burger exempted Petitioner from receiving further flu vaccines. Ex. 41 at 1. Her medical records on October 24, 2012 note that Petitioner has a suspected allergy to the flu vaccine. Ex. 2 at 1. This record further indicates that Petitioner has a permanent exemption from receiving the flu vaccine due to her history of hand numbness and tingling later diagnosed as MS two weeks after she received her flu vaccine. *Id.* Additionally, her medical records from the Mayo Clinic also indicate that Petitioner has an allergy to the flu vaccine. Ex. 4 at 3.

Dr. Steinman discussed this exemption at hearing. He testified that, "[h]er doctors, her treating, board certified doctors attribute the vaccine and the timing as a cause. They have exempted her from further vaccines." Tr. at 40. Dr. Vartanian also discussed Petitioner's exemption from the flu vaccine. He testified as follows:

> I think it's always a little hard to get into the head of a physician, trying to understand their reasoning, their choice. So it could be that that particular physician firmly believes that there is a causal relationship between the vaccine and the onset of her MS or causing her MS. The other possibility is that the physician recognizes Mrs. Robinson's very true and authentic fear of the vaccine and just doesn't want to put her through that vaccination even though he or she might think it's irrelevant.

Tr. at 190-91. Ultimately, while I have considered Dr. Vartanian's view on this issue, I decline to draw the inference that Dr. Burger gave Petitioner an exemption from the flu vaccine in order to save her from future anxiety. The plain reading of the medical records indicates that Dr. Burger believed it was medically appropriate that Petitioner no longer receive the flu vaccine.

While this evidence does not involve a treating physician articulating a theory of causation regarding how the flu vaccine caused Petitioner's MS, it still demonstrates that Dr. Burger believed the vaccine caused Petitioner's illness. I agree with Dr. Steinman's assessment and find that the opinion of Petitioner's treating neurologist is persuasive evidence with respect to whether Petitioner's flu vaccine did in fact cause her injury.

b. *Alternate Source of Injury*

Although Respondent does not contend that he has established an alternate cause of Petitioner's condition by preponderant evidence, he asks that I consider other potential sources of Petitioner's MS in making my determination as to whether Petitioner has provided preponderant evidence that the flu vaccine caused her condition. *See* Tr. at 27; *Stone v. Sec'y of Health & Hum. Servs.*, 676 F.3d 1373, 1379-80 (Fed. Cir. 2012) (finding that special masters can consider other possible sources of injury in making a determination under *Althen* prong two).

During the pendency of this case, Respondent has raised the issue of Petitioner's obesity, her female gender, her prior infection with EBV, and her use of sublingual immune therapy as risk factors that Petitioner possessed independent of her receipt of the flu vaccine.

Obesity, female gender, and prior infection with EBV are all risk factors for developing MS later in life. Zhou, et al., *Genetic loci for Epstein-Barr virus nuclear antigen-1 are associated*

with risk of multiple sclerosis, MSJ 1-10 (2016) (filed as Ex. N); Tettey, et al., *Frequency of Comorbidities and Their Association with Clinical Disability and Relapse in Multiple Sclerosis*, 46 NEUROEPIDEMIOLOGY 106-13 (2016) (filed as Ex. M); Hedström, et al., *Obesity interacts with infectious mononucleosis in risk of multiple sclerosis*, 22 EUROPEAN JOURNAL OF NEUROLOGY 578-84 (2015) (filed as Ex. E). Despite this association, it is difficult to draw any meaningful conclusions in Petitioner's case. As Dr. Vartanian stated, the influence of these factors "is rather small and of course there are many people who are obese, and had mononucleosis or evidence of EBV infection but do not have MS." First Vartanian Rep. at 7.

Respondent also raised sublingual immune therapy as a potential cause of Petitioner's MS. SLIT is a non-FDA approved allergy treatment where the patient receives drops of the allergen under her tongue in order to diminish the body's immune response. Tr. at 43. According to Dr. Vartanian, "one effect it has is on the induction of MicroRNA-146a (miRNA-146a)." First Vartanian Rep. at 16. miRNA-146a is "a sequence of a small piece of ribonucleic acid that was discovered about a decade and a half ago and has been shown to be a very important regulator of immune function and other functions in the body." Tr. at 44. Dr. Vartanian noted that MicroRNA-146a is increased after SLIT treatment. *See* Luo, et al., *Increased Expression of miR-146a in Children With Allergic Rhinitis After Allergen-Specific Immunotherapy*, 8 ALLERGY ASTHMA IMMUNOL RES. 132-40 (2016) (filed as Ex. H). Dr. Vartanian additionally noted that miRNA-146a is up-regulated in MS and thought to play a role in MS pathogenesis. Devier, et al., *Increase in NF-κB-sensitive miRNA-146a and miRNA-155 in multiple sclerosis (MS) and pro-inflammatory neurodegeneration*, 8 FRONTIERS IN MOLECULAR NEUROSCIENCE 1-5 (2015) (filed as Ex. C); Lescher, et al., *MicroRNA regulation in experimental autoimmune encephalomyelitis in mice and marmosets resembles regulation in human multiple sclerosis lesions*, 246 JOURNAL OF NEUROIMMUNOLOGY 27-33 (2012) (filed as Ex. G).

Dr. Steinman disagreed that SLIT therapy had anything to do with Petitioner's MS and instead opined that "SLIT therapy increases the amount of immune suppression in the body." Tr. at 48. According to Dr. Steinman, if SLIT therapy had any role with respect to Petitioner's immune response, "[i]t would be a beneficial role to make any inflammatory response milder." *Id.* at 57.

Both experts agree that MS is likely caused by a combination of genetics and environmental factors. *See also* Steinman & Oldstone: "[C]ertain genes conferring susceptibility to the disease and certain factors in the environment are both critical for the development of autoimmunity, and this is particularly true for multiple sclerosis." Steinman & Oldstone, *More mayhem for molecular mimics*, 3 NATURE MEDICINE 12, 1394-97 (1997) (filed as Ex. 32). Both experts also agree that the precise cause of MS is unknown. In his first report, Dr. Vartanian stated "at this time, it is accepted that we do not know enough about the pathophysiology of MS to say with any certainty that environmental factor X, Y or Z is causative for MS." First Vartanian Rep. at 7. During trial, Dr. Vartanian testified with respect to SLIT, "I just looked at it as another possible explanation and researched it and found some interesting facts." Tr. at 167. This testimony demonstrates that Respondent's evidence regarding SLIT therapy triggering MS is more of a hypothesis as opposed to a developed theory.

Petitioner testified that one of her treating doctors at the Mayo Clinic described her situation as the "perfect storm". Tr. at 26. Along these same lines, I do not view the existence of

Petitioner's risk factors as evidence that precludes a finding that the flu vaccine caused her illness. While I have considered the evidence of alternate cause in its totality, this evidence does not change my finding that the flu vaccine, more likely than not, *did cause* Petitioner's MS. Petitioner has presented preponderant evidence in support of the second *Althen* prong.

VII. Conclusion

Upon careful evaluation of all the evidence submitted in this matter, including the medical records, the testimony, as well as the experts' opinions and medical literature, I conclude that Petitioner has met her burden of proof under *Althen*. Accordingly, Petitioner is entitled to compensation. An order regarding damages will issue shortly.

IT IS SO ORDERED.

s/ Katherine E. Oler
Katherine E. Oler
Special Master